

AMERICAN SOCIETY OF HYPERTENSION SYMPOSIUM SERIES
VOLUME 1

Biologically Active Atrial Peptides

Editors

Barry M. Brenner, M.D.

*Laboratory of Kidney and Electrolyte Physiology
Brigham and Women's Hospital
and Harvard Medical School
Boston, Massachusetts*

John H. Laragh, M.D.

*Cardiovascular Center and Department of Medicine
Cornell University Medical College
New York, New York*

Raven Press  New York

671.192

Raven Press, 1185 Avenue of the Americas, New York, New York 10036

© 1987 by Raven Press Books, Ltd. All rights reserved. This book is protected by copyright. No part of it may be reproduced, stored in a retrieval system, or transmitted, in any form or recording, or otherwise, without the prior written permission of the publisher.

Made in the United States of America

Library of Congress Cataloging-in-Publication Data

Biologically active atrial peptides.

(American Society of Hypertension symposium series; v. 1)

Based on a symposium held May 31–June 1, 1986 in New York City.

Includes bibliographies.

I. Atrial natriuretic peptides—Congresses.

I. Brenner, Barry M., 1937– II. Laragh,

John H., 1924– III. Series. [DNLM:

1. Natriuretic Peptides, Atrial—congresses.

QU 68 B615 1986]

QP572.A86B56 1987 612'.12 86-42946

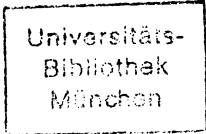
ISBN 0-88167-306-4

The material contained in this volume was submitted as previously unpublished material, except in the instances in which credit has been given to the source from which some of the illustrative material was derived.

Great care has been taken to maintain the accuracy of the information contained in the volume. However, Raven Press cannot be held responsible for errors or for any consequences arising from the use of the information contained herein.

Materials appearing in this book prepared by individuals as part of their official duties as U.S. Government employees are not covered by the above-mentioned copyright.

9 8 7 6 5 4 3 2 1



G 2 1987

Contents

Chapters

1	Functional Morphology of the Endocrine Component of the Heart <i>A. J. de Bold</i>	1
2	Expression and Regulation of the Gene for Atrial Natriuretic Peptide <i>D. G. Gardner, C. F. Deschepper, S. Hane, M. L. LaPointe, B. J. Gertz, W. F. Ganong, J. D. Baxter, and J. A. Lewicki</i>	3
3	Molecular Forms of Atrial Natriuretic Polypeptides Circulating in Human Plasma <i>H. Matsuo</i>	9
4	Molecular Forms of Atrial Natriuretic Factor <i>G. Thibault, R. Garcia, J. Gutkowska, J. Genest, and M. Cantin</i>	13
5	Distribution and Molecular Forms of Atrial Natriuretic Factor in Various Tissues <i>T. Inagami, T. Imada, R. Takayanagi, I. Tanaka, M. Naruse, R. J. Rodeheffer, and A. S. Hollister</i>	17
6	Characterization of Atrial Natriuretic Factor Released by Cultured Human Atrial Myocytes <i>M. J. F. Camargo, J. H. Laragh, and S. A. Atlas</i>	21
7	Atriopeptins: Secretion and Metabolism <i>N. Katsube, D. Schwartz, and P. Needleman</i>	27
8	Some Mechanisms of Release of Atrial Natriuretic Factor <i>R. Garcia, D. Lachance, G. Thibault, J. Gutkowska, and M. Cantin</i>	35
9	Physiological and Pathological Stimuli Releasing Atrial Natriuretic Peptide in Humans <i>J. V. Anderson and S. R. Bloom</i>	41

10	Atrial Natriuretic Peptide Receptor-Effector Coupling in Cultured Vascular Cells	49
	<i>J. A. Lewicki, D. B. Schenk, F. Fuller, G. McEnroe, L.-L. Kang, A. Arfsten, K. Schwartz, and R. M. Scarborough</i>	
11	Endocrine and Metabolic Effects of Atrial Natriuretic Peptides in Humans	55
	<i>J. Biollaz, B. Waeber, J. Nussberger, and H. R. Brunner</i>	
12	Studies on the Secretion, Metabolism, Regulation, and Action of Alpha Human Atrial Natriuretic Peptide in Humans: Evidence for an Endocrine Function in Health and Circulatory Disorders	65
	<i>E. A. Espiner, M. G. Nicholls, T. G. Yandle, I. G. Crozier, R. C. Cuneo, and H. Ikram</i>	
13	Atrial Natriuretic Peptide and Cardiovascular Redistribution in Humans	71
	<i>F. R. Bühler, F. B. Müller, A. E. G. Raine, P. Erne, W. Kiowski, L. Linder, T. J. Resink, and P. Bolli</i>	
14	Increased Resistance to Venous Return: Postulate for Atrial Natriuretic Factor—Induced Decrease in Cardiac Preload	81
	<i>N. C. Trippodo</i>	
15	Atrial Natriuretic Factor in Congestive Heart Failure	89
	<i>C. I. Johnston, L. Arnolda, K. Tsunoda, and P. Hodsman</i>	
16	Circulating Levels of Atrial Natriuretic Factor and the Response to Synthetic Atrial Natriuretic Factor (Auriculin B) in Patients with Chronic Congestive Heart Failure	97
	<i>R. J. Cody, S. H. Kubo, S. A. Atlas, K. S. Ryman, A. Shakhovich, and J. H. Laragh</i>	
17	Effects of Atrial Natriuretic Peptides on Glomerular Filtration, Peritubular Starling Forces, and Epithelial Sodium Transport	103
	<i>B. R. Dunn and B. M. Brenner</i>	
18	ANF-Induced Increase in Glomerular Filtration Rate and Decrease in Inner-Medullary Hypertonicity Are Important Determinants of ANF's Natriuretic Action	109
	<i>T. Maack</i>	
19	Can an ANF-Mediated Increase in Glomerular Filtration Rate by Itself Cause a Natriuresis?	119
	<i>M. G. Cogan, C.-L. Huang, F.-Y. Liu, and K. R. Wong</i>	

20	Effect of Atrial Natriuretic Factor on Collecting Duct Function	125
	<i>H. Sonnenberg</i>	
21	The Renal Papilla Is Necessary for the Full Effect of Atrial Natriuretic Factor	129
	<i>T. A. Fried, R. W. Osgood, and J. H. Stein</i>	

Extended Abstracts

Section I: Atrial Natriuretic Peptide Synthesis, Storage, and Release

Evidence for Atrial Peptide Localization in Hematopoietic Cells	133
<i>M. G. Currie, J. A. V. Simson, and R. P. Thompson</i>	
High Molecular Weight Precursors for Rat and Human Atrial Natriuretic Factors: Expression of Recombinant Proteins in <i>E. coli</i>	136
<i>P. O. Olins, C. S. Devine, E. Y. Wong, and M. L. Bittner</i>	
Hydrolysis of Atriopeptin-2 and Other Vasoactive Peptides by a Peptidyl Dipeptidase from Cultured Endothelial Cells	138
<i>J. J. Lanzillo, Y. Dasarathy, J. Stevens, and B. L. Fanburg</i>	
Intracellular Signals Regulating Atrial Natriuretic Peptide Secretion	141
<i>H. Ruskoaho, M. Toth, D. Ganten, Th. Unger, and R. E. Lang</i>	
Fetal Bovine Serum and Epinephrine Induce Release of Atrial Natriuretic Factor in Superfused Rat Atrial Myocytes	146
<i>G. E. Bilder, T. L. Schofield, C. F. Homnick, and E. H. Blaine</i>	
Effect of α - and β -Adrenergic Agonists and Antagonists on Atrial Natriuretic Peptide Secretion <i>in Vitro</i>	149
<i>T. Hattori, K. Hashimoto, H. Inoue, M. Sugawara, S. Suemaru, T. Takao, J. Kageyama, and Z. Ota</i>	
Water Deprivation and Atrial Natriuretic Factor in Normal and Brattleboro Rats: Effects of Water Drinking	152
<i>P. Januszewicz, J. Gutkowska, G. Thibault, R. Garcia, C. Mercure, F. Jolicœur, J. Genest, and M. Cantin</i>	
Fetal Rat Hypothalamic Cells Release a Sodium Transport Inhibitor, a Proinhibitor, and Atrial Natriuretic Peptide	154
<i>K. Morgan, M. Lewis, M. Scanlon, and M. A. Mir</i>	
Relation Between Atrial-Specific Granules and Cardionatrin Synthesis and Storage in the Rat	158
<i>O. E. Tadross, I. R. Sarda, P. L. Davies, and A. J. de Bold</i>	

Direct Effects of Right Atrial Pressure on Release of Atrial Natriuretic Peptide from Isolated Rat Heart <i>C. M. Saint-Come and J. C. S. Fray</i>	162
Identification of Atrial Natriuretic Factor-Like Immunoreactivity in the Frog Heart <i>P. Netchitailo, M. Feuilleley, G. Pelletier, M. Cantin, F. Leboulenger, A. De Léan, and H. Vaudry</i>	166
Atrial Natriuretic Peptide Secretion from the Isolated Rat Atria <i>H. Masuda, K. Nagai, K. Kangawa, and H. Matsuo</i>	170
Atrial Stretch-Secretion Coupling and Immunoreactive Cardionatrin Release <i>in Vitro</i> : Effect of Ca^{2+} and EGTA <i>M. L. de Bold and A. J. de Bold</i>	173
Time Course of Plasma Atrial Natriuretic Factor-Related Immunoactivity After Intravenous Bolus and Intranasal Administration of hANF 4-28 (WY-47,663) to Adult Female Rats <i>F. Bex, A. Corbin, K. Michalak, S. Luberti, G. Maenner, N. Wummer</i>	175
Atrial Natriuretic Peptide in the Dog: Distribution and Molecular Forms of iANP in Atria and Plasma $T_{1/2}$ of Infused ANP <i>P. Cernacek, E. Maher, J. C. Crawhall, and M. Levy</i>	179
Secretory Cycle of Atrial Myoendocrine Cells <i>W. G. Forssmann, D. Hock, G. Rippegather, P. Schultz-Knappe, K. Nokihara, and M. Reinecke</i>	182
Biologically Active Atrial Natriuretic Factor-Like Peptides in Peripheral Endocrine and Neuronal Tissues of the Rat <i>J. Gutkowska, W. Debinski, K. Racz, O. Kuchel, G. Thibault, R. Garcia, J. Genest, and M. Cantin</i>	185
Tissue Atrial Natriuretic Peptide: Immunoreactivity in Humans and in the Rat <i>G. B. M. Lindop, E. A. Mallon, G. D. McIntyre, and A. M. McNicol</i>	187
Phosphorylation of Atrial Natriuretic Peptides by Cyclic AMP-Dependent Protein Kinase <i>J. Rittenhouse, L. Moberly, M. E. O'Donnell, N. E. Owen, and F. Marcus</i>	192
Regulation of Vascular Membrane Phosphorylation by Cyclic Nucleotides, Sodium Nitroprusside, and Human Atrial Natriuretic Factor <i>P. J. Silver, S. M. Kocmund, and P. B. Pinto</i>	195
Processing of Atrial Natriuretic Factor by Atrial Thiol-Dependent Protease <i>J. H. Baxter, I. B. Wilson, and R. B. Harris</i>	199
Synthesis of a More Potent Atriopeptin III Analog <i>J. D. Morgannam, D. Chang, J. K. Chang, C. W. Xie, X. R. Li, D. L. Song, and J. Tang</i>	203
Influence of Fluid Volume and Systemic Arterial Pressure on Plasma Atrial Peptide Level <i>M. Gellai and M. G. Currie</i>	206

Atrial Natriuretic Polypeptide in Human Plasma and Tissue <i>K. Yoshinaga, K. Yamaguchi, K. Abe, Y. Miyake, K. Otsubo, S. Hori, M. Kusuhara, H. Oona, A. Kanai, K. Maruno, and Y. Mishima</i>	209
A Study on the Factors Affecting the Radioimmunoassay of Cardionatrin <i>I. R. Sarda and A. J. de Bold</i>	213
Effects of Plasma Volume Expansion on Plasma Atrial Natriuretic Factor <i>A. L. Rauch, M. Morris, and V. M. Buckalew, Jr.</i>	216
Isoproterenol Increases the Level of Plasma Immunoreactive Atrial Natriuretic Peptide in the Anesthetized Rabbit <i>A. J. Rankin, N. Wilson, and J. R. Ledsome</i>	219
Section II: Atrial Natriuretic Peptide Receptors and Second Messengers	
Identification of Atrial Natriuretic Factor Receptors and Atrial Natriuretic Factor-Induced Phosphorylation of Membrane Proteins <i>I. Sen and P. Roy</i>	223
Binding and Molecular Properties of Atrial Natriuretic Hormone Receptors from Rabbit Aorta, Renal Cortex, and Adrenal Tissue <i>W. Holleman, G. Budzik, E. Devine, V. Sarin, P. Connolly, T. Rockway, and E. N. Bush</i>	226
Specific Binding Sites of Atrial Natriuretic Factor (ANF) in Isolated Perfused Rat Kidney: Relationship with Renal Effects of ANF <i>M. Suzuki, D. Nussenzveig, D. Sawyer, F. A. Almeida, and T. Maack</i>	229
Binding Sites for Atrial Natriuretic Peptide in Tree Shrew and Primate Adrenal Glands <i>E. Fuchs, G. Flügge, K. Shigematsu, and J. M. Saavedra</i>	232
Atrial Natriuretic Peptide Binding Properties of Rat Glomerular Membranes <i>F. E. Cole, M. Hamada, H. A. Burmester, K. A. Graci, A. A. MacPhee, N. C. Trippodo, and E. D. Frohlich</i>	235
Effects of High- and Low-Sodium Diets on Atrial Natriuretic Binding to Renal Membranes and Glomeruli in Rats <i>M. F. J. Walsh, L. L. Rydstedt, S. Reddy, and J. R. Sowers</i>	239
Evidence for Atrial Natriuretic Factor Receptor Binding Sites in Bovine Brain Microvessels <i>P. E. Chabrier, P. Roubert, I. Viossat, F. Rodrigue, and P. Braquet</i>	242
Increased Atrial Natriuretic Peptide (99–126) Binding Sites in the Subfornical Organ of Water-Deprived Brattleboro Rats <i>J. M. Saavedra, A. Israel, F. M. A. Correa, and M. Kurihara</i>	244
Binding, Internalization, and Degradation of Atrial Natriuretic Factor in Cultured Leydig Tumor Cells <i>K. N. Pandey, K. S. Misono, and T. Inagami</i>	248
Influence of Atrial Natriuretic Factor Receptor-Initiated Phosphoinositide Metabolism and ^{22}Na Uptake in Arteries <i>S. Gupta, M. D. Campbell, E. J. Cragoe, Jr., and R. C. Deth</i>	252

Particulate Guanylate Cyclase: Target Enzyme of Atrial Natriuretic Factor <i>J. Tremblay, S. C. Pang, E. Schiffrin, J. Gutkowska, J. Cusson, P. Larochelle, and P. Hamet</i>	255
Atrial Natriuretic Factor Stimulation of Na/K/Cl Cotransport in Vascular Smooth Muscle Cells: Role of Cyclic GMP <i>M. E. O'Donnell and N. E. Owen</i>	258
Vascular Vasopressin Receptors Mediate Inhibition of Atrial Natriuretic Factor-Induced cGMP Accumulation <i>P. Nambi, M. Whitman, N. Aiyar, and S. T. Crooke</i>	260
Exposure of AtT-20 Corticotrophs to Atrial Natriuretic Factor (ANF) Results in Desensitization of ANF-Induced cGMP Formation and ANF Internalization <i>S. Heisler, E. Israël-Assayag, and G. Morel</i>	263
<i>In Vivo</i> Evidence that cGMP Is the Second Messenger for Atrial Natriuretic Factor <i>C.-L. Huang, H. E. Ives, and M. G. Cogan</i>	266
The Role of cGMP in the Inhibitory Action of Atrial Natriuretic Peptide on Aldosterone Secretion Stimulated by Angiotensin II <i>P. Q. Barrett, K. Zawulich, and C. M. Isaacs</i>	269
Effect of Atrial Natriuretic Factor on Adenylate Cyclase in Cultured Atrial and Ventricular Cardiocytes <i>M. B. Anand-Srivastava and M. Cantin</i>	272
Effects of a Synthetic Alpha-Human Atrial Natriuretic Polypeptide on Renal Function and the Production of Cyclic Nucleotide <i>K. Ito, T. Yukimura, T. Takenaga, H. Yamada, K. Miura, and K. Yamamoto</i>	275
Atrial Natriuretic Factor Suppresses cAMP Content of Human Fibroblasts Independent of the Inhibitory Guanyl Nucleotide-Binding Regulatory Component of Adenylate Cyclase <i>M. A. Lee, R. E. West, Jr., and J. Moss</i>	279

Section III: Atrial Natriuretic Peptide and the Endocrine System

The Anterior Pituitary Gland Modulates the Release of Atrial Natriuretic Peptides from the Cardiac Atria <i>N. Zamir, D. Lichtstein, M. Haass, Z. Zukowska-Grojec, H. Keiser, and S. Kassir</i>	283
Effect of Atrial Natriuretic Peptide on Urinary Kallikrein in Normal Humans <i>A. Mimran, J. Biollaz, J. Nussberger, B. Waeber, and H. R. Brunner</i>	287
The Effect of Atrial Natriuretic Factor on the Renin Angiotensin Axis <i>M. Takagi, M. Takagi, R. Franco-Saenz, and P. J. Mulrow</i>	290
Atrial Natriuretic Peptide Transcription, Secretion, and Glomerular Receptor Activity During Mineralocorticoid-Induced Volume Expansion <i>B. J. Ballermann, K. D. Bloch, J. G. Seidman, and B. M. Brenner</i>	293
Interactions of Atrial Natriuretic Factor, Angiotensin II, and Vasopressin on Various Target Cells <i>M. B. Vallotton, A. M. Capponi, P. D. Lew, R. P. Wuthrich, C. Wicht, and W. Dolci</i>	297

Atrial Natriuretic Peptide Inhibits Angiotensin II, ACTH, and Potassium-Stimulated Calcium Influx into Rat Adrenal Glomerulosa Cells <i>E. L. Schiffrin and L. Chartier</i>	302
Atrial Natriuretic Factor Attenuates Pressor Responses to Central Angiotensin II <i>S. L. Bealer, E. H. Blaine, and K. G. Proctor</i>	305
Atrial Natriuretic Peptide Inhibited a Hemorrhage-Induced ACTH Secretion <i>M. Sugawara, T. Hattori, K. Hashimoto, H. Inoue, S. Suemaru, T. Takao, J. Kageyama, and Z. Ota</i>	309
Role of Atrial Natriuretic Peptides in the Physiologic Regulation of Endocrine Systems in Conscious Dogs <i>C. H. Metzler, T. N. Thrasher, L. C. Keil, and D. J. Ramsay</i>	311
Inappropriately Elevated Levels of Atrial Natriuretic Peptide in Bartter's Syndrome May Explain the Pathophysiology <i>R. D. Gordon, T. J. Tunny, S. A. Klemm, and S. M. Hamlet</i>	315
Atrial Natriuretic Factor is an Inhibitory Modulator of Peripheral Sympathoadrenomedullary Activity <i>O. Kuchel, W. Debinski, K. Racz, M. T. Buu, A. De Léan, R. Garcia, M. Cantin, and J. Genest</i>	318

Section IV: Cardiovascular Actions of Atrial Natriuretic Peptide

Hemodynamic, Neurohumoral, and Renal Response to Atrial Natriuretic Peptide Infusion in the Conscious Dog <i>P. Carson, P. Carlyle, and J. N. Cohn</i>	322
Cardiac, Atrial Peptide, and Renal Responses to Acute Graded Volume Expansion <i>R. S. Zimmerman, B. S. Edwards, T. R. Schwab, D. M. Heublein, and J. C. Burnett, Jr.</i>	325
Cardiac Effects of Atrial Natriuretic Peptide <i>In Vivo</i> and <i>In Vitro</i> <i>J. C. Burnett, Jr., G. M. Rubanyi, B. S. Edwards, T. R. Schwab, R. S. Zimmerman, P. M. Vanhoutte</i>	328
Pharmacology of a Synthetic Human Atrial Natriuretic Factor, WY-47,663 <i>R. L. Wendt, P. J. Silver, J. L. Dinish, N. K. Metz, R. Michalak, J. A. Todt, R. W. Lappe</i>	330
A Comparison of the Vasorelaxant and Hemodynamic Properties of Synthetic Atriopeptins <i>R. L. Webb, G. R. Ghai, B. W. Barclay, R. D. Ghai, and M. B. Zimmerman</i>	335
Cardiovascular Effects Produced by Microinjection of a Fragment of Atrial Natriuretic Peptide into the Rat Preoptic Suprachiasmatic Nucleus <i>M. A. Sills and D. M. Jacobowitz</i>	339
The Inhibitory Profile of Atriopeptin III Against Various Agonists in the Isolated Renal Artery of the Rabbit <i>J. U. Weis</i>	342

Effect of Preload on the Release of Atrial Natriuretic Factor by the Isolated Heart-Lung Preparation from Dahl Rats <i>M. O. Onwohiei, R. M. Snajdar, and J. P. Rapp</i>	344
Antriopeptin III Interaction with Alpha-Receptor Subtypes and Their Pre-Versus Postsynaptic Functions <i>J. J. Kyncl, E. N. Bush, and S. A. Buckner</i>	347
Atriopeptin III Infusion Antagonizes Reflexive Increases in Plasma Norepinephrine in Conscious Rats <i>Z. Zukowska-Grojec, M. Haass, and N. Zamir</i>	351
Selective Attenuation of Angiotensin-Induced Vasoconstriction by Atrial Natriuretic Factor <i>K. G. Proctor, E. H. Blaine, and S. L. Bealer</i>	354
Synthetic Atrial Natriuretic Factor Potentiates Bradycardic Baroreflex Response in the Rabbit <i>M. Volpe, A. Cuocolo, F. Vecchione, A. F. Mele, M. Condorelli, and B. Trimarco</i>	358
Atrial Natriuretic Peptide and <i>In Vivo</i> Cell Na^+ and Ca^{2+} Handling <i>K. H. Le Quan Sang, G. Waeber, M. G. Pernollet, J. Nussberger, M. A. Devynck, B. Waeber, H. R. Brunner, and P. Meyer</i>	363
Antidipsogenic Action of Intracerebroventricularly Administered Atrial Natriuretic Polypeptides: Potencies and Sensitivities <i>H. Itoh, K. Nakao, G. Katsuura, N. Morii, S. Shiono, T. Yamada, A. Sugawara, Y. Saito, M. Sakamoto, A. Matsushita, and H. Imura</i>	367
Platelet-Activating-Factor-Induced Impairment of the Effects of Atrial Natriuretic Factor in Anesthetized Dogs <i>P. Thievaant, J. Baranes, and P. Braquet</i>	370
Acute Effects of Synthetic Atrial Natriuretic Factor in Anesthetized Spontaneously Hypertensive Rats and DOCA-Salt Hypertensive Rats <i>Y. Kasai, K. Abe, M. Yasujima, M. Tanno, M. Kohzuki, K. Yoshinaga, and S. Saso</i>	376
Atrial Natriuretic Factor Increases Hematocrit and Decreases Plasma Volume in Nephrectomized Rats <i>F. A. Almeida, M. Suzuki, and T. Maack</i>	379
Dose-Dependent and Permissive Effects of Atrial Natriuretic Factor in Water-Loaded Anesthetized Rats <i>F. Spinelli, B. Kamber, and C. Schnell</i>	383
Atrial and Plasma Atrial Natriuretic Factor in Experimental Heart Failure in the Rat <i>G. P. Hodsman, K. Tsunoda, and C. I. Johnston</i>	385
Hematocrit Is Increased by Atrial Natriuretic Peptide in Nephrectomized Rats <i>J. P. Flückiger, B. Waeber, G. Matsueda, J. Nussberger, and H. R. Brunner</i>	388
Plasma Atrial Natriuretic Factor Levels Increase Postprandially in the Dog Following a High-Sodium Meal <i>K. M. Verburg, R. H. Freeman, J. O. Davis, D. Villarreal, and R. C. Vari</i>	390

Section V: Renal Actions of Atrial Natriuretic Peptide

Effects of Atrial Natriuretic Factor on Autoregulation of Renal Blood Flow in Innervated and Denervated Kidneys <i>R. W. Lappe, J. A. Todt, and R. L. Wendt</i>	394
Effects of a Synthetic Atrial Natriuretic Polypeptide on Intrarenal Hemodynamics in Dogs <i>Y. Abe, T. Tamaki, K. Fukui, S. Fujioka, A. Yamamoto, Y. Fujisawa, and H. Iwao</i>	398
Atrial Natriuretic Factor Inhibits Ca^{2+} -Dependent K^+ Fluxes in Vascular Smooth Muscle and Renal Glomerular Cells <i>R. P. Garay, P. Hannaert, C. Bianchi, M. Cantin, P. Meyer, J. Genest, and P. Braquet</i>	401
Atrial Natriuretic Peptide Modulates Isolated Rat Glomeruli Contraction <i>J. M. López-Novo, G. Arriba, A. Fernandez-Cruz, L. Hernando, and D. Rodríguez-Puyol</i>	403
Angiotensin II and Hyperoncotic Albumin Modulate the Natriuresis Induced by Atrial Natriuretic Peptide <i>R. E. Mendez, B. R. Dunn, J. L. Troy, and B. M. Brenner</i>	406
Inhibitory Effect of Atrial Natriuretic Peptides on Chlorine Absorption in Loops of Henle Perfused <i>In Vivo</i> <i>J. P. Briggs, H. Velazquez, G. Schubert, M. Marin-Grez, and J. Schnermann</i>	410
Renal Interstitial Hydrostatic Pressure Dynamics During Atrial Natriuretic Peptide Administration <i>T. R. Schwab, B. S. Edwards, R. S. Zimmerman, D. M. Heublein, and J. C. Burnett, Jr.</i>	413
Effect of Atrial Natriuretic Peptide on Hydraulic Pressures in the Rat Renal Papilla <i>B. R. Dunn, I. Ichikawa, and B. M. Brenner</i>	416
Atrial Natriuretic Peptide and Amiloride Inhibit Apical Na^+ Flux in Cultured Rabbit Inner Medullary Collecting Duct Cells <i>M. L. Zeidel, J. L. Seifter, B. M. Brenner, P. Silva, and S. Sariban-Sohraby</i>	420
Role of cGMP in Atrial Natriuretic Peptide Inhibition of Na^+ Transport by Rabbit Inner Medullary Collecting Duct Cells <i>M. L. Zeidel, P. Silva, B. M. Brenner, and J. L. Seifter</i>	422
The Renal Dopamine System Mediates the Diuretic/Natriuretic Effect of Atrial Natriuretic Peptide <i>A. Pettersson, J. Hedner, and T. Hedner</i>	426
Vasopressin Dissociates the Responses of Sodium and Water Excretion to Atrial Natriuretic Factor in Water-Diuretic Rats <i>J. P. Briggs and J. Schnermann</i>	428
Secretion of Atrial Natriuretic Peptides and Renal Responses to Hypervolemia and Exogenous Atriopeptin in Nephrotic Rats <i>R. Keeler, D. Feuchuk, and N. Wilson</i>	432

Section VI: Clinical Physiology and Pharmacology

Atrial Natriuretic Polypeptide Secretion and Central Hemodynamics in Humans <i>A. Sugawara, K. Nakao, K. Nishimura, N. Morii, M. Sakamoto, T. Yamada, H. Itoh, S. Shiono, Y. Saito, T. Ban, and H. Imura</i>	436
Angiotensin II Infusion Increases Plasma Atrial Natriuretic Hormone in Normal Subjects, but Nifedipine Blocks This Increase <i>G. H. Anderson, Jr., M. Miller</i>	439
The Role of Atrial Natriuretic Polypeptide in the Pathogenesis of Escape from the Mineralocorticoid Excess <i>I. Miyamori, M. Ikeda, and R. Takeda</i>	443
Immunoreactive Atrial Natriuretic Peptide in Human Plasma: Modulation by Dietary Sodium Intake <i>G. A. Sagnella, N. D. Markandu, A. C. Shore, and G. A. MacGregor</i>	447
Pharmacodynamic Effects of Bolus Administration of Atrial Natriuretic Factor in Normal Volunteers <i>P. Larochelle, J. Cusson, P. Hamet, P. Du Souich, E. Schiffrin, J. Genest, and M. Cantin</i>	451
The Antirenin Angiotensin Action of Atrial Natriuretic Peptide in Humans <i>F. B. Müller, P. Bolli, P. Erne, A. E. G. Raine, T. J. Resink, L. Linder, and F. R. Bühler</i>	455
Atrial Natriuretic Peptide and Head-Out Water Immersion in Humans <i>J. V. Anderson, N. D. Millar, J. P. O'Hare, J. C. MacKenzie, R. J. M. Corrall, and S. R. Bloom</i>	459
Renal Site of the Effect of Atrial Natriuretic Peptide In Humans <i>J. Biollaz, J. Bidiville, J. Diezi, B. Waeber, J. Nussberger, H. R. Brunner, F. Brunner-Ferber, and H. J. Gomez</i>	462
Changes Caused by Plasma Atrial Natriuretic Peptide During Postnatal Adaptation <i>T. Tulassay and W. Rascher</i>	465
Human Platelet-Rich and Platelet-Poor Plasma Atrial Natriuretic Peptide Levels During Dehydration <i>D. M. Heublein, T. R. Schwab, B. S. Edwards, R. S. Zimmerman, D. W. Heser, P. C. Kao, and J. C. Burnett, Jr.</i>	467
Relationship Between Atrial Natriuretic Factor and Left Atrial Pressure and Dimension in Humans <i>H. Kurihara, K. Hara, K. Kuwako, T. Yamaguchi, M. Isobe, M. Ishibashi, and T. Yamaji</i>	469
Dissociation Between Atrial Natriuretic Peptide Release and Atrial Pressure During Cardiac Pacing in Humans <i>A. E. G. Raine, P. Erne, E. Burgisser, and F. R. Buhler</i>	473

Section VII: Experimental Pathophysiology

Circulating Natriuretic Peptide Levels in Rats with Myocardial Infarction <i>P. Wilkes, H. Mandin, P. Keane, J. Kirstein, T. Wong, and M. O'Connor</i>	477
---	-----

Atrial Natriuretic Factor Levels in a Hamster Model for Congestive Heart Failure <i>F. Bex, R. Lappe, K. Michalak and A. Corbin</i>	481
Atrial Natriuretic Peptide During the Development of Heart Failure in Conscious Dogs <i>A. J. G. Riegger, E. P. Kromer, S. Wild, M. Hofbauer, and K. Kochsiek</i>	484
Atrial Natriuretic Peptide in Pulmonary Hypertension Resulting from Repeated Embolism in Conscious Rats <i>A. J. G. Riegger, P. Hoferer, E. P. Kromer, and K. Kochsiek</i>	486
Circulating Levels of Atrial Natriuretic Factor Are Elevated in Rats with Experimental High-Output Heart Failure <i>A. Haramati, J. C. Burnett, A. Hoffman, and J. Winaver</i>	490
Changes in Specific Receptor Binding of Atrial Natriuretic Peptides in Spontaneously Hypertensive Rat Kidney <i>T. Ogura, T. Mitsui, I. Yamamoto, E. Katayama, Z. Ota, and N. Ogawa</i>	493
Decreased Number and Affinity of Rat Atrial Natriuretic Peptide (99-126)-Binding Sites in the Subfornical Organ of Spontaneously Hypertensive Rats <i>J. M. Saavedra, A. Israel, M. Kurihara, and F. M. A. Correa</i>	495
Elevated Circulating Levels of Atrial Natriuretic Factor in Cardiomyopathic Hamsters <i>H. A. Franch, L. A. Heinel, L. T. Callahan, E. H. Blaine</i>	499
Effect of Long-Term Treatment with Nisoldipine on Atrial Natriuretic Peptides and Prevention of Hypertension in Spontaneously Hypertensive Rats <i>J.-P. Stasch, S. Kazda, C. Hirth, A. Knorr, F. Morich, and D. Neuser</i>	503
Effects of Chronic Salt Loading on Plasma Atrial Natriuretic Peptide in Spontaneously Hypertensive Rats with Atrial Appendectomy <i>K. Gradin, J. Hedner, T. Hedner, and B. Persson</i>	506
Effect of Antihypertensive Therapy on Plasma and Cardiac Concentration of Atrial Natriuretic Peptides in Spontaneously Hypertensive Rats <i>M. Kohno, T. Matsuura, H. Inariba, K. Yasunari, K.-I. Murakawa, T. Nishikimi, and T. Takeda</i>	509
Reduced Increment in Circulating Atrial Natriuretic Peptides After Volume Expansion in Young Spontaneously Hypertensive Rats <i>M. Haass, N. Zamir, D. S. Goldstein, I. J. Kopin, and Z. Zukowska-Grojec</i>	512
Atrial Natriuretic Peptide in the Spontaneously Hypertensive Rat: Plasma Levels and Renal Effects <i>J. P. Granger and M. Awazu</i>	516
Chronic Effect of Synthetic Atrial Natriuretic Factor in Rats Made Hypertensive by Sustained Infusion of Vasopressin <i>M. Yasujima, K. Abe, M. Kohzuki, M. Tanno, Y. Kasai, M. Sato, K. Takeuchi, K. Omata, and K. Yoshinaga</i>	519
Atrial Natriuretic Factor and Plasma Catecholamines in Rats with Acute and Chronic Renal Failure <i>E. S. Marks, P. Ohman, D. S. Goldstein, N. Zamir, and H. R. Keiser</i>	523

Section VIII: Clinical Pathophysiology

Human Atrial Natriuretic Peptide: Plasma Levels and Hemodynamic, Hormonal, and Renal Effects in Patients with Heart Failure <i>A. J. G. Riegger, E. P. Kromer, and K. Kochsiek</i>	527
Atrial Natriuretic Peptide and Cyclic GMP Levels in Healthy Children and in Children with Cardiac Diseases <i>J. Weil, R. Gerzer, C. Döhlemann, K. Bühlmeier, F. Bidlingmaier, T. Strom, and R. E. Lang</i>	531
Circulating Atrial Natriuretic Polypeptide During Exercise in Patients with Valvular Heart Disease <i>T. Nishikimi, M. Kohno, T. Matsuura, K. Akioka, M. Teragaki, M. Yasuda, H. Oku, K. Takeuchi, and T. Takeda</i>	534
Plasma Levels of Atrial Natriuretic Factor in Cardiac Arrhythmia and Congestive Heart Failure <i>H. Nakaoka, K. Imataka, Y. Kitahara, and J. Fujii</i>	537
Tachycardia-Induced Natriuresis and Atrial Natriuretic Peptide <i>J. V. Anderson, J. S. R. Gibbs, E. Rowland, N. N. Payne, J. D. H. Slater, and S. R. Bloom</i>	541
Differential Processing of Plasma Atrial Natriuretic Factor in Cardiovascular Disease <i>R. M. Arendt, A. L. Gerbes, D. Ritter, and E. Stangl</i>	544
Rapid Variation in Plasma Atrial Natriuretic Peptide During Cardiopulmonary Bypass Surgery <i>J. Hedner, A. C. Towle, R. A. Mueller, Saltzmann, I. A. Norfleet, C. B. Watson, and T. Hedner</i>	548
Stimulation of Plasma Atrial Natriuretic Factor in Cirrhotic Humans by Immersion-Induced Central Hypervolemia <i>M. Epstein, R. Loutzenhiser, E. Friedland, R. Aceto, M. J. F. Camargo, and S. Atlas</i>	552
Effect of Head-Out Water Immersion on Plasma Atrial Natriuretic Peptide Levels in Cirrhotics with Ascites <i>A. Fernandez-Cruz, D. Rodriguez-Puyol, J. Gutkowska, and J. M. López-Novoa</i>	555
Primary Aldosteronism, Recumbent Posture, and Salt Loading Are Associated with Higher Levels of Atrial Natriuretic Peptide <i>T. J. Tunny, S. A. Klemm, S. M. Hamlet, and R. D. Gordon</i>	558
The Regulation of Atrial Natriuretic Peptides During Chronic Hemodialysis <i>R. R. Barager, M. M. Batenjany, K. D. Wilner, D. M. Ward, and M. G. Ziegler</i>	561
A Study of Plasma Atrial Natriuretic Polypeptide in Patients Undergoing Hemodialysis <i>O. Iimura, K. Shimamoto, M. Nakagawa, T. Ando, Y. Yamaguchi, and A. Masuda</i>	564

Alpha Atrial Natriuretic Content of Human Cord Blood in Cesarean Section and Normal Vaginal Delivery	567
<i>J. M. Stewart, G. A. Zeballos, M. Mohyuddin, B. K. Rajegowda, P. K. Woolf, and M. H. Gewitz</i>	
Immunoreactive Atrial Natriuretic Peptide Levels in a Volume-Expanded Black Patient Population	571
<i>S. N. Barakat, M. F. J. Walsh, S. Zuireck, J. V. Felicetta, and J. R. Sowers</i>	
Postural Changes in Atrial Natriuretic Peptide in Hypertensive and Normal Subjects: Effect of Varying Sodium Intake	574
<i>M. F. Walsh, S. N. Barakat, M. B. Zemel, S. M. Gualdoni, and J. R. Sowers</i>	
Plasma Atrial Natriuretic Peptide in Patients with Mild to Moderate Essential Hypertension	577
<i>T. Hedner, J. Hedner, A. C. Towle, M. Hartford, S. Ljungman, K. Caidahl, O. Andersson, J. Wikstrand, and G. Berglund</i>	
Sodium Intake and Posture Modulate Plasma Atrial Natriuretic Peptide in Normotensive and Hypertensive Humans	582
<i>G. Wambach, S. Götz, G. Suckau, G. Bönner, and W. Kaufmann</i>	
Increased Plasma Levels of Atrial Natriuretic Peptide in Patients with Untreated Essential Hypertension	585
<i>G. A. MacGregor, G. A. Sagnella, N. D. Markandu, A. C. Shore, D. R. J. Singer, and F. P. Cappuccio</i>	
Effect of Human Atrial Natriuretic Peptide in Hypertensive Male Patients and Healthy Men	588
<i>A. Korn, H. Vierhapper, W. Waldhäusl, and P. Nowotny</i>	
Effects of Alpha-Human Atrial Natriuretic Peptide in Essential Hypertension During Converting Enzyme Inhibition	592
<i>E. Agabiti-Rosei, M. Beschi, M. Castellano, and G. Muiesan</i>	
Cardiorenal Actions of Atrial Natriuretic Peptide in Angiotensin II Hypertension	595
<i>B. S. Edwards, T. R. Schwab, R. S. Zimmerman, D. M. Heublein, and J. C. Burnett, Jr.</i>	
Hemodynamic, Renal, and Endocrine Responses to Alpha-Human Atrial Natriuretic Polypeptide in Normotensive Persons and Patients with Essential Hypertension	598
<i>M. Ishii, T. Sugimoto, H. Matsuoka, Y. Hirata, T. Ishimistu, K. Fukui, T. Sugimoto, K. Kangawa, and H. Matsuo</i>	
Pharmacodynamics of Infusions of Atrial Natriuretic Factor in Normotensive and Hypertensive Subjects	602
<i>J. R. Cusson, P. Hamet, J. Gutkowska, O. Kuchel, J. Genest, M. Cantin, and P. Larochelle</i>	
The Antihypertensive Effect of Long-Term Infusions of Atrial Natriuretic Peptide in Essential Hypertension	606
<i>P. E. de Jong, W. M. T. Janssen, G. K. van der Hem, and D. de Zeeuw</i>	

Pregnancy-Induced Hypertension and Preeclampsia Develop in Spite of Raised Circulating Levels of Cardionatriin <i>P. Fievet, A. Fournier, A. de Bold, N. El Esper, I. Gregoire, A. Idrissi, and M. Herve</i>	609
Plasma Atrial Natriuretic Peptide and Vasopressin in Preeclampsia <i>N. Wilson, D. Miller, and D. F. Farquarson</i>	612
<i>Subject Index</i>	615

DIFFERENTIAL PROCESSING OF PLASMA ATRIAL NATRIURETIC FACTOR IN CARDIOVASCULAR DISEASE

Rainer M. Arendt, Alexander L. Gerbes, Detlef Ritter, and
Elisabeth Stangl

*Departments of Medicine I and II, Ludwig-Maximilian-University,
Klinikum Grosshadern, 8000 Munich, Federal Republic of Germany*

The recent discovery of the long-elusive natriuretic hormone, atrial natriuretic factor (ANF), has emphasized the importance of the heart in blood pressure regulation and volume homeostasis (1). Its smallest endocrine unit is the atrial myoendocrine cell (2), the biological function of which is determined by (a) substrate uptake, (b) biosynthesis of the pre-prohormone, (c) cleaving of the signal peptide, (d) storage of the prohormone in specific granules, and, upon the appropriate stimulus, (e) secretion of the biologically active material by exocytosis. Under normal conditions, the posttranslational processing of the prohormone is likely to be coupled to the secretion stimulus and may occur at the secretion site. We have recently demonstrated the presence of the processing product ANF-28 in the circulation of normotensive subjects (3). Surprisingly, it has also been shown that patients with cardiovascular disease characterized by volume/pressure loading have plasma levels of ANF that are considerably higher than those of their normotensive counterparts (3–6). Cirrhotic patients showing a similarly increased extracellular volume, though mainly confined to an extravascular subcompartment, also tended to have increased plasma levels, though not significantly so in all studies (7–9). Head-out water immersion has recently been shown to be an important investigative tool in the examination of the secretory function of the heart (10,11). In addition to alterations in stimulus-response coupling, a defective posttranslational processing of pro-ANF (ANF-126) or a modified target-tissue responsiveness to circulating ANF might

be important features in the pathophysiology of volume homeostasis. We have recently demonstrated that the molecular weight pattern of plasma ANF in hypertensive patients differs from that seen in normotensive controls (4). Elevated plasma ANF levels in patients with congestive heart failure consisted predominantly of such higher molecular weight forms not apparent in normal subjects (12). In this study, we document plasma levels of ANF in hypertensive patients, patients with congestive heart failure before and under converting-enzyme-inhibitor therapy, and in normotensive subjects and cirrhotic patients prior to and during head-out water immersion. An initial structural analysis of circulating ANF was achieved by use of high-performance gel permeation chromatography of plasma extracts from these patients.

METHODS

Extraction of plasma samples and radioimmunoassay procedures were modified from ref. 3. Briefly, antibody Toni III was used instead of the less sensitive antibody Toni II. This antibody is mid-molecule- and C-terminal-directed. Cross-reactivity with the N-terminally extended cardiodilatin-88 (gift from Dr. W. G. Forssmann, Heidelberg, Federal Republic of Germany) was 29.7%, 35.8% to rat ANF 28, 13% to atriopeptin III, and 0.03% to atriopeptin I or II. It did not cross-react with a wide variety of peptides and proteins, including its immunization conjugate, which is bovine thyroglobulin. The final titer was 1:120,000 and the assay sensitivity was 0.5 fmol/assay tube. The 50%-binding intercept of the standard curve was 7 fmol. Synthetic standards and iodinated labels were from NovaBiochem, Läufelfingen, Switzerland. Plasma aliquots (0.5–3 ml) were extracted by adsorption to pre-rinsed Anberlite XAD-2 adsorbent resin (particle size 0.3–1.0 mm, Serva, Heidelberg, Federal Republic of Germany) (3). Recovery of synthetic ANF-28 was approximately 67%. Levels were not yet corrected for recovery (the results of the "International Collaborative Study of the Proposed International Standard for Atrial Natriuretic Factor On Behalf of The AHA/ISH/WHO" pending). The intra-assay coefficient of variation ($n = 6$) was <5%. Plasma extracts (5 ml) were subjected to high-performance gel permeation chromatography on a 7.5×600 -mm TSK-125 Bio Sil column (Bio Rad, Munich, Federal Republic of Germany) and eluted with 0.09% trifluoroacetic acid containing 0.005 M Na_2SO_4 plus 0.002 M NaH_2PO_4 with 30% acetonitrile as a solvent. Flow rate was 0.4 ml/min, and aliquots from column fractions were analyzed for immunoreactive ANF (ir-ANF). Peripheral blood was drawn into precooled syringes and immediately transferred to precooled polystyrene tubes containing 500 KIU/ml aprotinin and 1 mg/ml sodium EDTA. Plasma was separated and stored at -70°C until extraction. Forty-one normotensive control subjects showing no evidence of cardiovascular, renal, pulmonary, or gastrointestinal disease took part in the study. Twenty-seven patients with essential hypertension were examined; at the time of examination, their mean blood pressure was 176 ± 4.1 over 101 ± 3.5 mm Hg. In addition, 14 patients with congestive heart failure functional class NYHA II to IV were studied. Patients were hospitalized 1 week before catheterization of the heart, and all medication was discontinued except for diuretics and digitalis. Measurements were taken before, immediately following, and 6 months after institution of therapy with an angiotensin-converting-enzyme inhibitor (enalapril, usually 5 mg twice daily). Thirty-one patients with cirrhosis of the liver, confirmed by biochemical and histological examination, were investigated. Cirrhotic patients were divided into subgroups with and without ascites. Twelve healthy controls and 11 cirrhotic patients were subjected to head-out water immersion procedures. After voiding, subjects assumed a seated position next to the immersion tank for the first hour of the experiment. Subsequently, they were immersed up to their necks, maintaining the same seated position in thermoneutral water ($34.0 \pm 0.2^\circ\text{C}$) for 1 hr, followed by an additional hour sitting outside the tank. Throughout the experiment, 250 ml/hr of tap water

was given orally. All patients were on a hospital diet allowing 150 mmol of NaCl daily. Experimental protocols were approved by the institutional committee on the ethics of human investigation.

RESULTS AND DISCUSSION

Hypertensive patients displayed a sevenfold increase in plasma ANF as compared to normotensive controls (62.2 ± 16.8 versus 8.8 ± 1.1 fmol/ml, mean \pm SEM, $p < 0.001$, Student's *t*-test). A subgroup of untreated patients with essential hypertension had comparably high levels. Patients with congestive heart failure displayed an 18-fold increase in plasma ANF (158 ± 56 fmol/ml, $p < 0.001$). Plasma ANF levels in cirrhotic patients (10.3 ± 1.3 fmol/ml) were not lower than in normotensive controls. Plasma ANF levels in congestive heart failure patients were positively and significantly correlated to increased right atrial pressure and pulmonary capillary wedge pressure ($r = +0.72$, $p < 0.01$; and $r = +0.73$, $p < 0.01$, respectively) and reversely related to cardiac index ($r = -0.73$, $p < 0.01$). In the course of 6 months' therapy with an angiotensin-converting-enzyme inhibitor (enalapril), plasma ANF levels in congestive heart failure patients fell, in parallel with the hemodynamic improvement, to 63% of pretreatment levels (from 158 ± 56 to 100 ± 50 fmol/ml, $p < 0.02$, Wilcoxon paired-sample test). Head-out water immersion induced an increase in plasma ANF levels by 83% following 1 hr of immersion (from 6.5 ± 0.8 to 12.0 ± 2.6 fmol/ml, $p < 0.01$). This response was comparable to that seen in cirrhotic patients without ascites, whereas cirrhotic patients with ascites displayed a blunted response (a 50% increase as compared to a 98% increase in patients without ascites) (9). An initial structural analysis of plasma ANF was performed by use of high-performance gel permeation chromatography in all plasma extracts. As previously reported (3), in normotensive individuals, ir-ANF consisted exclusively of authentic 3,080-dalton ANF-28, the biologically active processing product of pro-ANF (13). Such a molecular analysis in cirrhotic patients yielded a similar

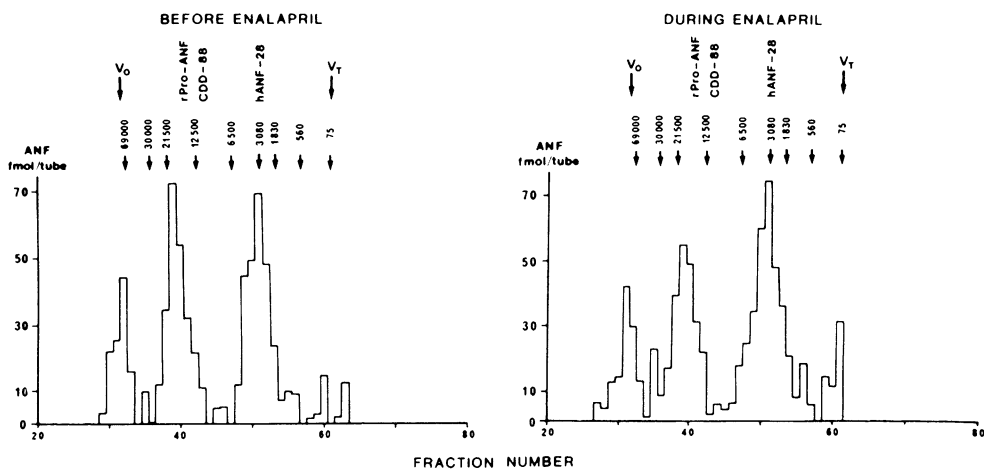


FIG. 1. Molecular weight pattern of ir-ANF in the plasma of a representative patient with congestive heart failure before and following institution of therapy with enalapril. The TSK-125 Bio Sil column was calibrated with bovine serum albumin (V_0), leu-enkephalin (V_T), a series of opioid peptides, and synthetic ANF-28. Fraction aliquots were assayed for ANF-immunoreactivity.

pattern. However, in these patients, trace amounts of a higher-molecular-weight material (~13,000 daltons) was also present. This higher-molecular-weight portion of plasma ir-ANF did not increase in parallel to the rise in authentic ANF-28 induced by head-out water immersion in cirrhotic patients. This finding is in favor of the contention that in these patients the stimulus-response coupling is intact and a maximal converting capacity of the putative pro-ANF-converting enzymes is not exceeded. Ir-ANF in hypertensive patients comprised a peak coeluting with synthetic ANF-28 as in normotensive subjects and cirrhotics; in addition, a 13,000-dalton-ANF immunoreactivity and an ANF immunoreactivity eluting in the void volume (molecular weight > 50,000 daltons) were also present. The void-volume ANF immunoreactivity most likely represents ANF-28 bound to carrier proteins (a differential recovery of which may, in part, explain the vast differences between various extraction procedures and between extracted and unextracted assays). The elevated plasma ANF levels in congestive heart failure were primarily composed of such higher-molecular-weight forms (Fig. 1). Interestingly, therapy with an angiotensin-converting-enzyme inhibitor effected a reduction in total plasma ANF immunoreactivity in parallel with a hemodynamic improvement. Molecular weight analysis revealed that it was primarily the higher-molecular-weight forms that were decreased rather than the authentic ANF-28. This may indicate that the increased demand in these patients that cannot be met, subsequently leading to the release of immature ANF forms. We conclude that a putative dysregulation of posttranslational processing of pro-ANF may be an important feature in the pathophysiology of cardiovascular disease states.

REFERENCES

1. Needleman, P., and Greenwald, J. E. (1986): *N. Engl. J. Med.* 314:828-834.
2. Forssmann, W. G. (1986): *Eur. J. Clin. Invest.* (in press).
3. Arendt, R. M., Stangl, E., Zähringer, J., Liebisch, D. C., and Herz, A. (1985): *FEBS Lett.*, 189:57-61.
4. Arendt, R. M., Gerbes, A. L., Ritter, D., Stangl, E., Bach, P., and Zähringer, J. (1986): *J. Hypertens.*, 4(Suppl. 2).
5. Richards, A. M., Nicholls, M. G., Espiner, E. A., et al. (1985): *Hypertension*, 7:812-817.
6. Burnett, J. C. Jr., Kao, P. C., Hu, D. C., et al. (1986): *Science*, 231:1145-1147.
7. Gerbes, A. L., Arendt, R. M., Ritter, D., Jüngst, D., Zähringer, J., and Paumgartner, G. (1985): *N. Engl. J. Med.*, 313:1609-1610.
8. Epstein, M. (1986): *Hepatology*, 6:312-315.
9. Gerbes, A. L., Arendt, R. M., Riedel, A., et al. (1986): *Gastroenterology*, 90:1727.
10. Gerbes, A. L., Arendt, R. M., Schnizer, W., et al. (1986): *Klin. Wochenschr.* (in press).
11. Epstein, M., Loutzenhiser, R. D., Friedland, E., Aceter, R. M., Camargo, M. J. F., and Atlas, S. A. (1986): *J. Hypertens.*, 4(Suppl. 2).
12. Arendt, R. M., Ritter, D., Gerbes, A. L., and Zähringer, J. (1986): *Clin. Res.*, 34:626A.
13. Nakayama, K., Ohkubo, H., Hirose, T., Inayama, S., and Nakanishi, S. (1984): *Nature*, 310:699-701.